II. NON-TECHNICAL ABSTRACT:

The prostate has become the leading site of internal malignancy in men. Prostate cancer will be responsible for approximately 41,800 cancer deaths in U.S. men in 1997. The incidence and mortality rates are higher in African American men than in any population in the world. Since prostate cancer incidence increases more rapidly with age than any other tumor and the average age of American men is increasing, the number of patients with prostate cancer and the number of deaths from the disease are expected to rise steadily into the next century.

Current therapies for localized prostate cancer include surgical removal of the prostate (radical prostatectomy) or local irradiation. Many patients who undergo a radical prostatectomy are clinically understaged. Patients with positive surgical margins, seminal vesical invasion, or positive lymph nodes are at increased risk for disease recurrence and shortened survival. Treatment failures are usually signified by a rising prostate specific antigen (PSA) level and may represent either local or distant recurrence. New perioperative adjuvant therapies are needed to enhance the cure rate in these patients with clinically localized disease. Consequently, we believe the risk associated with this gene therapy approach in these patients is offset by the potential significant therapeutic benefit of reducing or possibly eliminating the cancer.

Direct introduction of therapeutic genes into tumor cells may provide an effective treatment of prostate tumors. One strategy is to confer drug sensitivity to tumor cells by inserting a recombinant gene into them. This gene is from the common Herpes virus and codes for the enzyme thymidine kinase (HSV-tk). Thymidine kinase converts the anti-viral drug ganciclovir into a form that is toxic to rapidly dividing cells such as tumor cells. Non-dividing cells are not harmed. This approach is especially suitable for the treatment of prostate tumors since the normal prostate tissue is made up largely of non-dividing cells. Several techniques have been used to introduce therapeutic genes into tumors. Of these, virus-mediated transfer is currently the most efficient method and the most efficient virus is the genetically engineered adenovirus. We have demonstrated using human and animal models for prostate cancer that adenovirus-mediated transfer of the HSV-tk gene and ganciclovir treatment results in ablation of the tumors as well as in suppression of metastatic disease.

This phase I/II protocol is designed to study the safety and efficacy of gene therapy for patients with clinically localized prostate cancer and poor prognostic indicators for disease recurrence. There is currently no standard adjuvant therapy when used with radical prostatectomy. Thus, the potential risks associated with the use of gene therapy in this group would appear reasonable. Patients with clinically localized prostate cancer and poor prognostic indicators will be treated with intra-tumoral injection of a replication-defective adenovirus vector delivering the Herpes Simplex Virus thymidine kinase gene. Initial tests will use a low dose of vector. Ganciclovir will then be administered intravenously at 10 mg/kg/day for 14 days. Only one course of therapy will be administered. Each patient will be carefully monitored for adverse effects. A radical prostatectomy will be performed 2 weeks after the last dose of intravenous ganciclovir. The primary objective of this study is to gain insight into the distribution of the vector in the prostate and the biological effects on the tumor, while continuing to assess the safety of this regimen. By continuing to monitor these patients over several years, we hope to assess the impact of this therapy on cancer progression rates in comparison with historic anc concomitant matched controls.